REMARKS

By the present amendment, claim 4 has been amended to clarify that the claimed method is a method of treating a body fluid containing a transforming growth factor-β, comprising removing the transforming growth factor-β from the body fluid. Further, new claim 7 depends on claim 4 and recites that the body fluid is contacted with the adsorbent extracorporeally, new claim 8 corresponds to previously presented claim 4 and additionally recites that the body fluid is returned to the body, and new claim 9 depends on claim 8 and recites that the method is incorporated into an extracorporeal circulation circuit used in combination with another extracorporeal circulation therapy. Support for new claims 7-9 is found in the original application, in particular on page 13, lines 15-26.

Claims 3-4 and 6-9 are pending in the present application. Independent claim 4, and claims 3 and 6-7 dependent thereon, are directed to a method for therapeutic treatment of a body fluid containing a transforming growth factor-β. Independent claim 8, and claim 9 dependent thereon, are directed to a method for removing a transforming growth factor-β from a body fluid.

As a preliminary, Applicants and Applicants' representative thank the Examiner for the Personal Interview held on December 10, 2003.

In the Office Action, claims 3-4 are rejected under 35 U.S.C. 103(a) as obvious over either of US 4774322 (Seyedin et al.), US 4931548 (Lucas) or US 5322933 (Davies), in view of US 5,231,178 to Holtz et al. (Holtz) and further in view of US 6270994 (Miyazono).

It is alleged in the Office Action that each of the first three references Seyedin, Lucas, and Davies, discloses isolating TGF-β using reverse-phase chromatography with a C-18 column, that the Miyazono reference provides a motivation to remove TGF-β from body fluid because it

discloses that TGF-β is associated with various conditions, so that it would be beneficial to "reduce TGF-β activity" in body fluids, and that Holtz suggests the use of porous cellulose because Holtz discloses purification of another growth factor, IGF-1, by HPLC using a cellulose support.

The rejection is respectfully traversed. As has been made clear by the present amendment, the method of claims 3-4 and 6-7 is a method of treating a body fluid containing a transforming growth factor-β, comprising removing the transforming growth factor-β from the body fluid, including the step recited in claim 4. This method is not taught or suggested in the cited references.

Specifically, the three references Seyedin, Lucas, and Davies are not directed to the therapeutic treatment of body fluid, but to the isolation of TGF-β from a starting composition after a series of processing steps. There is no indication in these three references that such methods might be adaptable to the treatment of body fluid by removing TGF-β from the body fluid, and there is no suggestion to modify the isolation methods of these references in order to treat body fluid by bringing the body fluid in contact with the adsorbent.

The same is true with respect to the newly cited Holtz reference. The carrier used in Holtz is for purification of proteins from a pretreated fermentation broth. Holtz considers that pretreatment is essential (see Holtz at col. 20, lines 10-12), and the pretreatment includes the preparation of a cell-free composition (see Holtz at col. 23, line 57).

Further, the Miyazono reference discloses a connection between TGF-β and various diseases, but Miyazono completely fails to teach of suggest addressing these diseases by treating body fluid to remove TGF-β from the body fluid. Rather, Miyazono suggests reducing TGF-β activity inside the body by modulating signal transduction in cells (see Miyazono at col. 20, lines 14-20). Accordingly, a person of ordinary skill in the art would not infer from Miyazono that

TGF-β should be removed from body fluid, but only that TGF-β activity should be modulated, for example, by the addition of a modulator as proposed by Miyazono (see Miyazono at col. 20, lines 44-48). As a result, Miyazono does not provide any suggestion or motivation for treating body fluid by removing TGF-β from body fluid.

In contrast, the present inventors have discovered that an adsorbent comprising (i) a porous cellulose carrier, and (ii) a compound immobilized on said carrier and having a log P value of at least 2.50, wherein P is a partition coefficient in an octanol-water system, is adapted for the removal of TGF-β by bringing the body fluid in contact with the adsorbent, and further, that this removal step can be applied to the treatment of body fluid containing TGF-β by removing TGF-β from the body fluid. This treatment method is not taught or suggested in any of the cited references, since Seyedin, Lucas, and Davies as well as Holtz are limited to the isolation methods described therein, and Miyazono is silent regarding addressing problems connected to TGF-β by treating body fluid in order to remove TGF-β from the body fluid.

In addition, the porous cellulose used in the presently claimed invention can provide important strength, selectivity, and safety advantages, as indicated on page 10, lines 11-25 of the present specification. These advantages are unexpected in particular from the newly cited Holtz reference, since the carrier used in Holtz is for purification of proteins from a pretreated cell-free composition, and Holtz is silent as to which adsorbent or carrier would be suitable to remove TGF-β from body fluid.

Further, with respect to present claims 8-9, it is submitted that none of the cited references teaches or suggests a method of removing TGF-β from body fluid wherein the body fluid is returned to the living body. Specifically, the isolation methods of Seyedin, Lucas, and Davies as

well as Holtz eliminate any possibility of returning body fluid to the body, in particular since water, solvents and reagents are used in these methods. Further, Miyazono is directed to modulation of TGF-β in the body, not removal of body fluid from the body, removal of TGF-β from the body fluid, and returning the body fluid to the body.

In contrast, an advantage of the present invention as claimed in claims 8-9 is that it allows direct contact of body fluid with the adsorbent without dilution by water and solvent and without contamination by a reagent, so that the body fluid may be applied to blood purification in which the body fluid is returned to the living body, as recited in present claim 8. These features and advantages of the method of claims 8-9 are not taught in any of the cited references.

In view of the above, the present claims are not obvious over the cited references taken alone or in any combination. Therefore, it is submitted that the rejection should be withdrawn.

In conclusion, the invention as presently claimed is patentable. It is believed that the claims are in allowable condition and a notice to that effect is earnestly requested.

In the event there is, in the Examiner's opinion, any outstanding issue and such issue may be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

In the event this paper is not considered to be timely filed, the Applicants hereby petition for an appropriate extension of the response period. Please charge the fee for such extension and any other fees which may be required to our Deposit Account No. 50-2866.

Respectfully submitted,

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